## REMARKS

**Status of the Claims.**

Claims 1-23 and 51-67 are pending in the present application. Claims 2, 3, 14, 16-18, 52, 53, 57-59, 61, and 62 have been amended, and claims 65-67 have been added.

Support for the amendments is as follows. The claims have been amended to even more clearly recite the invention, to ensure consistent use of terminology throughout the claims, and to correct informalities. Support for the amendments to claims 14 and 16 and for claims 65-67 can be found throughout the specification, *e.g.*, at page 3, line 3 – page 4, line 3 and at page 4, lines 12-25. Support for the amendment to claim 58 is found at least at page 38, line 25 – page 39, line 3 and page 39, lines 9-19. Therefore, the amendments do not introduce new matter.

**Claim Objection.**

The Examiner objected to claims 15 and 16 because the Examiner believed that these claims were duplicates of one another. Applicants respectfully point out that claim 15 recites a composition "that comprises a recombinant cell-specific ***binding moiety***," whereas claim 16 recites a composition "a recombinant ***binding moiety-encoding nucleic acid***." As these claims are not duplicates, Applicants respectfully request withdrawal of the objection.

**35 U.S.C. § 112, Second Paragraph.**

Claims 2-23 and 51-64 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Office Action, at page 3. The rejection is respectfully traversed.

The Examiner found claim 2(1) indefinite with respect to "which form of nucleic acid encodes a nucleic acid binding domain or whether another form of nucleic acid encodes" this domain. *Id.* The Examiner also found this section indefinite with respect to "which form of nucleic acid encodes a cell-specific ligand or whether another form of nucleic acid encodes a cell-specific ligand." *Id.* Claim 2(1) has been amended to recite:

> recombining at least first and second forms of at least one nucleic acid, ***wherein each of the first and second forms of the nucleic acid comprises a polynucleotide that encodes a nucleic acid binding domain*** and at least first and second forms of at least one additional nucleic acid, ***wherein each of the first and second forms of the additional nucleic acid comprises a polynucleotide that encodes a***

***cell-specific ligand that specifically binds to a protein on the surface of a cell of interest . . . .***

The Examiner found claims 18(1) confusing on the same ground, and claim 18(1) has been similarly amended.

Claim 2(2) was found indefinite because the Examiner stated that there was no antecedent basis for the recited library of vectors and further that "[i]t is unclear what 'library of vectors' is intended." Office Action, page 3. Applicants note that because this section recited "***a*** library of vectors," antecedent basis was not an issue. However, to expedite prosecution, claim 2(2) has been amended to recite "producing a library of vectors from the library of recombinant binding moiety-encoding nucleic acids, wherein each vector comprises: a) a binding site specific for the nucleic acid binding domain and b) a member of the library of recombinant binding moiety-encoding nucleic acids." As the Examiner indicated that claim 18(2) unclear for the same reason, claim 18(2) has been similarly amended.

The Examiner found claim 2(3) and claim 3(8) indefinite on the ground that it was "unclear where the 'expressed recombinant binding moiety'" comes from because the 'expressed recombinant binding moiety' has not been recovered from the transfected cells." *Id.* Claims 2 and 3 have been amended to add new sections (3) and (9), respectively, which recite this recovery. A similar issue in claim 18(3) has been added by adding new section (3).

The Examiner found claim 2(5) and claim 3(9) indefinite because of the phrase "determining if one or more target cells contains a vector." *Id.* Specifically, the Examiner questioned whether the "vector" recited in this phrase was the "vector-binding moiety complex." Office Action, page 4. This phrase has been amended to read: "determining if one or more target cells contain a vector from the vector-binding moiety complex."

The Examiner stated that the term "vaccine antigen" in claims 51, 53 and 64 was vague and rendered the claims indefinite. These claims have been amended to recite "polypeptide antigen."

The Examiner found claims 17 and 59 indefinite because of clear grammatical errors, which have been corrected.

Applicants point out that none of the amendments discussed above in connection with the § 112, second paragraph, rejection change the scope of any claim. Applicants submit that the

pending claims are clear and definite and respectfully request withdrawal of the § 112, second paragraph, rejection.

**35 U.S.C. § 112, First Paragraph.**

Claims 51-58 and 64 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that "the specification . . . , does not reasonably provide enablement for a method of producing and screening [for] a cell-specific binding moiety that could fuse to, link to, or coat on any vaccine antigen other than the polynucleotide comprising the nucleic acid binding site." Office Action, page 6. The rejection is respectfully traversed.

The rejected claims include method claims 51-57 and 64 as well as composition claim 58. Claim 51 is an independent claim reciting a method for producing and screening a recombinant cell-specific binding moiety polypeptide for an ability to increase uptake, efficacy, or specificity of a polypeptide antigen for a target cell." The remaining rejected method claims depend from claim 51. Claim 58 recites a composition for eliciting an immune response that includes "an antigen and a recombinant cell-specific binding moiety polypeptide, wherein the composition is produced by the method of claim 51."

The rejection is based on the recitation in claim 51(5) of "fusing or linking the recombinant cell-specific binding moiety polypeptide to the polypeptide antigen or coating the polypeptide antigen with the recombinant cell-specific binding moiety polypeptide." In explaining the rejection, the Examiner stated:

> The claims encompass any type of vaccine antigen that includes a DNA, RNA, a peptide, a polypeptide, a polysaccharide, or any molecule or cell that can stimulate an immune response in a host for vaccination purposes. The cell-specific binding moiety encoded by a polynucleotide encompasses binding activity to a polynucleotide or a polypeptide. The specification of the present application only teaches the binding of a cell-specific binding moiety containing a nucleic acid binding domain to a polynucleotide comprising a binding site for said nucleic acid binding domain. . . . It is unclear how a cell-specific binding moiety polypeptide, having any binding activity, would fuse to, link to, or coat on a DNA, RNA, . . . polypeptide, . . . polysaccharide, or any molecule or cell that can stimulate an immune response in a host for vaccination.

Office Action, page 7. As the pending claims recite that the antigen is polypeptide, the Examiner's statements relating to nucleic acids or polysaccharides are moot. With respect to polypeptide

antigens, it appears that the Examiner has interpreted claim 51 as if the recombinant cell-specific binding moiety polypeptide must be capable of binding directly to the recited antigen.

However, claim 51 recites, as an active step, fusing, linking, or coating the cell-specific binding moiety polypeptide to/on a polypeptide antigen. As one skilled in the art recognizes, claim 51(5) encompasses an embodiment in which the cell-specific binding moiety polypeptide contains a domain that binds to a cognate domain in a polypeptide antigen. Numerous examples of protein-protein binding were known as of the priority date of the application. Therefore, Applicants submit that, in light of the general guidance provided in the specification, one skilled in the art could produce a cell-specific binding moiety polypeptide that includes a fused or linked domain that binds to a polypeptide antigen. The resultant polypeptide could be conveniently produced as a fusion polypeptide, for example. The production of fusion proteins is discussed throughout the application and techniques for the production of fusion proteins were, in any case, within the level of skill in the art as of the priority date of the present application.

Additionally, claim 51(5) encompasses an embodiment in which the cell-specific binding moiety polypeptide is fused or linked with the polypeptide antigen itself by, for example, expressing the two as a fusion protein or otherwise chemically linking the two. As stated above, the production of fusion proteins was generally within the level of skill in the art as of the application's priority date. Also within the level of skill in the art at the time was the chemical linkage of polypeptides to other polypeptide or non-polypeptide components. Given a wide variety of methods and reagents for conjugating proteins to one another or to other components, Applicants submit that one skilled in the art could select methods and reagents suitable for a particular application of the invention.

Thus, the application enables one skilled in the art to join the cell-specific binding moiety polypeptide to the polypeptide antigen by any number means, some of which may employ other reagents or components, such as linkers. Accordingly, there is no reason that claim 51 should recite that the cell-specific binding moiety polypeptide inherently contains the means for joining this polypeptide to the polypeptide antigen.

As claims 51-58 and 64 are appropriately tailored to the disclosure in the specification, withdrawal of the § 112, first paragraph, rejection is respectfully requested.

**35 U.S.C. § 103(a).**

Claims 1, 14-16, and 58 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Stemmer et al. (WO97/20078) in view of Ledley et al. (WO94/25608) and Patten et al. (Current Opinion in Biotechnology (1997) 8:724-733). Office Action, page 8. This rejection is respectfully traversed.

In explaining the rejection, the Examiner stated that "Stemmer teaches a method for the production of nucleic acid fragments or polynucleotides encoding mutant proteins by repeated cycles of mutagenesis, shuffling and selection of nucleic acids to generate polynucleotides having desired characteristic [*sic*] by iterative selection and recombination for the molecular evolution *in vitro* or *in vivo* of proteins (e.g. abstract)." Office Action, at pages 8-9. The Examiner is of the view that "Stemmer does not teach generating a chimeric recombinant DNA comprising a DNA binding domain and a ligand which binds to the surface of a target cell." Office Action, page 9.

The Examiner cited Ledley as teaching "generating a chimeric recombinant DNA-binding protein comprising a first element for binding to a receptor on a target cell and a second element required for binding to DNA." Office Action, page 9. The Examiner also noted that Ledley teaches "a complex for gene transfer comprising a DNA molecule specifically and non-specifically bound to the chimeric recombinant DNA-binding protein (e.g. p. 26, 27, abstract)." *Id.*

Finally, the Examiner cited Patten's statement that "viral vaccine vectors can be enhanced by DNA shuffling to give desired properties of tropism, stability and expression level" as well as Patten's reference to "opportunities for DNA shuffling as a tool for increasing the efficiency and success rate of the development of novel whole organism, viral, bacterial and recombinant protein vaccines." Patten, page 732; *see* Office Action, page 9.

Applicants respectfully submit that the Examiner has not established a prima facie case of obviousness for any of claims 1, 14-16, or 58. To establish a *prima facie case* of obviousness, the Office must demonstrate that: (1) the cited reference or references teach or suggest every element of the claimed invention; (2) there is some suggestion in a particular cited reference or combination of cited references to modify the cited reference or to combine the teachings of the cited references to arrive at the claimed invention; and (3) there is a reasonable expectation of success in carrying out or arriving at the claimed invention based on the teachings of the cited references.

Distinctions over the cited references are described below for each rejected independent claim. In the interest of brevity, the following remarks focus on the Ledley and Patten

references because the Examiner relied on these references as teaching the application of the Stemmer methods to vaccines. *See* Office Action, at page 9. The Examiner will, of course, appreciate that Applicants' remarks relate to the cited combination of references over which the claims were rejected. Simply dismissing Applicants' arguments as directed to the references individually would therefore be inappropriate.

***Claim 1***

Claim 1 relates to a "method for producing and screening a cell-specific binding molecule for an ability to increase uptake or specificity of a genetic vaccine for a target cell." Claim 1 recites:

> creating a library of recombinant polynucleotides by recombining at least one nucleic acid that encodes a polypeptide that comprises a nucleic acid binding domain and at least one nucleic acid that encodes a polypeptide that comprises a cell-specific binding domain.

As noted above, the Examiner relies on Ledley as teaching this element of claim 1. Ledley teaches "a chimeric recombinant DNA-binding protein comprising a first element for binding to a receptor on a target cell and a second element required for binding to DNA." Ledley, at page 13, line 35 to page 14, line 1. Suitable first elements are described in Ledley at page 14, line 35 to page 15, line 24. Ledley contains general disclosures regarding how the disclosed chimeric proteins are produced. *See* page 10, lines 7-18 and page 16, lines 5-7.

Ledley does not, however, teach or suggest "creating a library of recombinant polynucleotides" by recombining a nucleic acid encoding one desired function, such as a nucleic acid binding domain, with another nucleic acid encoding a different desired function, such as a cell-specific binding domain. Nor can this teaching be found in Patten. According to the Examiner, however, it "would have been obvious for one of ordinary skill in the art at the time of the invention to substitute the first and second forms of polypeptide sequences taught by Stemmer with polynucleotide sequences encoding a DNA-binding element and a ligand binding . . . [element] as taught by Ledley for the production of a genetic vaccine as taught by Patten." *Id.*

However, the Examiner has failed to demonstrate how the cited references teach or suggest "creating a library of recombinant polynucleotides" by recombining two different nucleic acids that each encode a ***different*** polypeptide domain having a ***different*** function. Recombinant polynucleotides created in this manner encode polypeptides containing ***two different functional***

***domains that did not exist together in either polypeptide***. This recombination is thus different from that carried out to optimize a polynucleotide for a single function.

Because the Examiner has failed to identify all elements of the claimed invention in the cited references, no *prima facie* case of obviousness has been established with respect to claim 1.

Furthermore, the Examiner has failed to demonstrate that there is any suggestion in a particular cited reference or combination thereof to combine their teachings to arrive at the invention defined by claim 1. Based on the teachings of Ledley and Patten, the Examiner takes the position that one of ordinary skill at the time of the invention would have been motivated to produce and identify a cell-specific binding molecule having an ability to increase uptake or specificity of a genetic vaccine to a target cell, as set forth in claim 1. The Examiner states that one of skill would have been motivated to make such a cell-specific binding molecule because such a molecule "*could* facilitate the efficiency of gene transfer and the effects of a genetic vaccine to stimulate immune in a host." Office Action, p. 10. In drawing this conclusion, the Examiner appears to rely on Patten. Notably, however, Patten simply stated that DNA shuffling could be a "tool for increasing the efficiency and success rate of the development of ... recombinant protein vaccines." Patten did not teach or suggest using DNA shuffling to produce cell-specific binding molecules with abilities to increase uptake or specificity of a genetic vaccine. Nor did Patten suggest the development of any molecules that might facilitate gene transfer or enhance the effects of a genetic vaccine.

The Examiner has failed to demonstrate any suggestion in any of the cited references to combine the teachings to arrive at the claimed invention. For at least these reasons and those discussed above, Applications respectfully submit that no *prima facie* case of obviousness has been established with respect to claim 1.

***Claims 14, 15 and 16***

Claim 14 recites a "recombinant cell-specific binding moiety produced by expressing in a host cell a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2." According to claim 2, this nucleic acid is derived from the recombination of at least two forms of a nucleic acid comprising a polynucleotide that encodes a nucleic acid binding domain and at least two forms of an additional nucleic acid comprising a polynucleotide that encodes a cell-specific ligand. Claim 14 further recites that the claimed recombinant cell-specific binding moiety comprises "(i) a DNA binding domain . . ." and "(ii) a cell-specific ligand that confers on the recombinant cell-

specific binding moiety ***an enhanced ability to bind to the target cell***, as compared to the cell-specific ligand encoded by the first and second forms of the additional nucleic acid."

Claim 15 recites a "composition for eliciting an immune response that comprises the cell-specific binding moiety of claim 14" and thus incorporates the requirement that the cell-specific binding moiety include a DNA binding domain in combination with a cell-specific ligand that confers "an enhance ability to bind to the target cell." This element is also present in claim 16, which recites a "composition for eliciting an immune response that comprises a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2." Claims 65-66 also include this element.

In the Office Action, the Examiner noted that "the method of making a composition does not carry weight in the 103(a) rejection of the composition claims." Office Action, page 10. However, Applicants respectfully point out that the Examiner is not free to disregard method steps that constrain the structure of the resultant composition. Here, binding moiety of claim 14 would, as a result of how it is produced, include a functional cell-specific ligand and a functional nucleic acid binding domain derived from one of those recited in 14. Furthermore, the cell-specific ligand of the binding moiety recited in claims 14-15 and 65-67 has enhanced target cell binding, relative to the original cell-specific ligands encoded by the nucleic acids that were recombined to generate the recited binding moiety.

Ledley teaches the combination of "a DNA binding element and a ligand binding element," but Ledley fails to teach or suggest any modification of the ligand binding element for any purpose. *See, e.g.,* Ledley, page 7, lines 12-19; page 14, lines 12-15; page 14, line 35 – page 15, line 1; page 15, lines 19-21.

The Examiner has identified no binding moieties that combine an enhanced cell-specific ligand with a functional nucleic acid binding domain in any of the references of record. Therefore, Applicants submit that the rejection cannot be maintained.

***Claim 58***

Claim 58 recites:

A composition for eliciting an immune response comprising an antigen and a recombinant cell-specific binding moiety polypeptide, wherein the composition is produced by the method of claim 51, wherein:

(i) the antigen comprises a polypeptide antigen;

(ii) the cell-specific binding moiety polypeptide exhibits enhanced ability to bind to the target cell; and

(iii) the polypeptide antigen and the recombinant cell-specific binding moiety polypeptide are derived from different polypeptides.

Claim 51 recites that the cell-specific binding moiety polypeptide is fused or linked to or coated on the antigen. *See* Claim 51(5). Thus, claim 58 recites a composition in which an ***enhanced cell-specific binding polypeptide is fused or linked to, or coated on, a heterologous polypeptide antigen***.

Ledley teaches a chimeric protein that comprises a ligand binding element, but this element is linked to a DNA-binding element, not a polypeptide antigen. Ledley's chimeric protein is intended for use in targeting DNA vectors for use in gene therapy. Ledley teaches that protein/DNA complexes useful in gene therapy should not be antigenic. *See* Ledley, page 2, line 35 – page 3, line 2. Thus, Ledley teaches squarely away from a cell-specific binding polypeptide is fused or linked to, or coated on, a heterologous polypeptide ***antigen***. In addition, as discussed above, Ledley neither teaches nor suggests a ligand binding element that exhibits ***an enhanced capacity to bind to a target cell***.

The Examiner has identified no compositions that combine an enhanced cell-specific binding moiety polypeptide with a heterologous protein antigen in any of the references of record. Therefore, Applicants submit that the rejection cannot be maintained.

As the Office Action fails to show that the cited references teach or suggest all of the elements of claims 1, 14-16 and 58, withdrawal of the § 103 rejection is respectfully requested.

**Conclusion**

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If, after reviewing this Amendment, the Examiner believes that any of the pending claims are not in condition for allowance, an Examiner Interview is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

LAW OFFICES OF JONATHAN ALAN QUINE
P.O. BOX 458
Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877

Respectfully submitted,

Emily M. Haliday
Reg. No: 38,903

## APPENDIX A

## "MARKED UP" CLAIMS ILLUSTRATING THE AMENDMENTS MADE TO THE CLAIMS OF 09/247,866 WITH ENTRY OF THIS AMENDMENT

2. (Twice Amended) A method for producing and screening a recombinant cell-specific binding moiety for an ability to increase uptake or specificity of a genetic vaccine for a target cell, the method comprising:

(1) recombining at least first and second forms of at least one nucleic acid, wherein each of the first and second forms of the nucleic acid [which] comprises a polynucleotide that encodes a nucleic acid binding domain and at least first and second forms of at least one additional nucleic acid, wherein each of the first and second forms of the additional nucleic acid [which] comprises a polynucleotide that encodes a cell-specific ligand that specifically binds to a protein on the surface of a cell of interest, wherein the first and second forms of each nucleic acid differ from each other in two or more nucleotides, to produce a library of recombinant binding moiety-encoding nucleic acids;

(2) producing [introducing into one or more host cells one or more members of] a library of vectors from the library of recombinant binding moiety-encoding nucleic acids, wherein each vector [,each of which] comprises: a) a binding site specific for the nucleic acid binding domain and b) a member of the library of recombinant binding moiety-encoding nucleic acids;

(3) introducing one or more members of the library of vectors into one or more host cells, wherein the encoded recombinant binding moiety is expressed and recovering the expressed recombinant binding moiety;

(4) [(3)] binding the expressed recombinant binding moiety to a vector comprising the binding site to form a vector-binding moiety complex;

(5) [(4)] contacting the vector-binding moiety complex with a target cell of interest; and

(6) [(5)] determining if one or more target cells contain a vector from the vector-binding moiety complex , and recovering the recombinant cell-specific binding moiety nucleic acid from any such target cells.

3. (Twice Amended) The method of claim 2, wherein the method further comprises:

(7) [(6)] recombining at least one recombinant binding moiety-encoding nucleic acid of (6) [(5)] with a further form of the polynucleotide that encodes a nucleic acid binding domain and/or a further form of the polynucleotide that encodes a cell-specific ligand, which are the same or different from the first and second forms, to produce a further library of recombinant binding moiety-encoding nucleic acids;

(8) producing [(7) introducing into one or more host cells one or more members of] a further library of vectors from the further library of recombinant binding moiety-encoding nucleic acids, wherein each vector in the further library of vectors [, each of which] comprises: a) a binding site specific for the nucleic acid binding domain and b) a member of the further library of recombinant binding moiety-encoding nucleic acids;

(9) introducing one or more members of the further library of vectors into one or more host cells, wherein the encoded recombinant binding moiety is expressed and recovering the expressed recombinant binding moiety;

(10) [(8)] binding the expressed recombinant binding moiety of (9) to a vector comprising the binding site to form a vector-binding moiety complex;

(11) [(9)] contacting the vector-binding moiety complex of (10) with a target cell of interest and determining if one or more target cells contain a vector from the vector-binding moiety complex of (10);

(12) [(10)] recovering the recombinant binding moiety-encoding nucleic acid from any such target cells of (11); and

(13) [(11)] repeating (7) [(6)] through (12) [(10)] to screen for a cell-specific binding moiety useful for increasing uptake or specificity of a genetic vaccine vector for a target cell.

14. (Twice Amended) A recombinant cell-specific [recombinant] binding moiety produced by expressing in a host cell a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2, wherein the recombinant cell-specific binding moiety comprises:

(i) [the nucleic acid binding domain is] a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an E. coli CAP protein, myc,

a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a $Cys_3His$ (SEQ ID NO:6) box or the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV tat and HIV rev; and

(ii) a cell-specific ligand that confers on the recombinant cell-specific binding moiety an enhanced ability to bind to the target cell, as compared to the cell-specific ligand encoded by the first and second forms of the additional nucleic acid.

16. (Twice Amended) A composition for eliciting an immune response that comprises a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2, wherein the recombinant cell-specific binding moiety comprises:

(i) [the nucleic acid binding domain is] a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an E. coli CAP protein, myc, a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a $Cys_3His$ (SEQ ID NO:6) box or the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV tat and HIV rev; and

(ii) a cell-specific ligand that confers on the recombinant cell-specific binding moiety an enhanced ability to bind to the target cell, as compared to the cell-specific ligand encoded by the first and second forms of the additional nucleic acid.

17. (Twice Amended) A composition for eliciting an immune response that comprises:

a) a recombinant binding moiety that comprises a nucleic acid binding domain and a cell-specific ligand, and

b) a polynucleotide sequence that is capable of expressing an antigen and that comprises a binding site, wherein the nucleic acid binding domain is capable of specifically binding to the binding site.

18. (Three Times Amended) A method for producing and screening a recombinant cell-specific binding moiety for an ability to increase uptake, efficacy, or specificity of a vaccine or antigen for a target cell, the method comprising:

(1) recombining at least first and second forms of at least one nucleic acid, wherein each of the first and second forms of the nucleic acid [that] comprises a polynucleotide which encodes a binding moiety of an enterotoxin, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant nucleic acids;

(2) producing [introducing one or more members of] a library of vectors from the library of recombinant nucleic acids, wherein each vector [, each of which] comprises a member of the library of recombinant nucleic acids; [,]

(3) introducing one or more members of the library of vectors into one or more host cells, wherein the member of the library of recombinant nucleic acids is expressed to form a recombinant cell-specific binding moiety polypeptide and recovering the recombinant cell-specific binding moiety polypeptide;

(4) [(3)] contacting the recombinant cell-specific binding moiety polypeptide with a cell surface receptor of a target cell; and

(5) [(4)] determining if the recombinant cell-specific binding moiety polypeptide exhibits enhanced ability to bind to the target cell.

51. (Amended) A method for producing and screening a recombinant cell-specific binding moiety polypeptide for an ability to increase uptake, efficacy, or specificity of a polypeptide [vaccine] antigen for a target cell, the method comprising:

(1) recombining at least first and second forms of at least one nucleic acid that comprises a polynucleotide which encodes a cell-specific binding moiety, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant nucleic acids;

(2) introducing one or more members of a library of vectors, each of which comprises a member of the library of recombinant nucleic acids, into one or more host cells, wherein the member of the library of recombinant nucleic acids is expressed to form a recombinant cell-specific binding moiety polypeptide;

(3) contacting the recombinant cell-specific binding moiety polypeptide with a cell surface receptor of a target cell;

(4) determining if the recombinant cell-specific binding moiety polypeptide exhibits enhanced ability to bind to the target cell; and

(5) fusing or linking the recombinant cell-specific binding moiety polypeptide to the polypeptide [vaccine] antigen or coating the polypeptide [vaccine] antigen with the recombinant cell-specific binding moiety polypeptide.

53. (Amended) The method of claim 51, wherein the recombinant cell-specific binding moiety polypeptide is fused or linked to the polypeptide [vaccine] antigen.

57. (Twice Amended) A method for producing a composition for eliciting an immune response, said method comprising coating the polypeptide [an] antigen with a recombinant cell-specific binding moiety polypeptide produced by the method of claim 51.

58. (Twice Amended) A composition for eliciting an immune response comprising an antigen and a recombinant cell-specific binding moiety polypeptide, wherein the composition is produced by the method of claim 51, wherein:

(i) the antigen comprises a polypeptide antigen;

(ii) the recombinant cell-specific binding moiety polypeptide exhibits enhanced ability to bind to the target cell; and

(iii) the polypeptide antigen and the recombinant cell-specific binding moiety polypeptide are derived from different polypeptides.

59. (Amended) The method of claim 2, wherein the binding site of each vector is derived from a binding site present in at least [on] one form of at least one nucleic acid of (1).

61. (Amended) The method of claim 2, wherein the vector-binding moiety complex forms inside the host cell and, prior to the contacting of (5) [(4)], the host cell is lysed under conditions that do not disrupt the vector-binding moiety complex.

62. (Amended) The method of claim 3, wherein the vector-binding moiety complex of (10) [(8)] forms inside the host cell and, prior to the contacting of (11) [(9)], the host cell is lysed under conditions that do not disrupt the vector-binding moiety complex.

63. The method of claim 2, wherein the cell-specific ligand comprises a polypeptide derived from a protein selected from the group consisting of CD2, CD28, CTLA-4, CD40, and ligands therefor; fibrinogen; factor X; ICAM-1; β-glycan; Fc portion of immunoglobulin G; and a bacterial enterotoxin, or a subunit thereof.

--65. A recombinant cell-specific binding moiety produced by expressing in a host cell a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2, wherein the recombinant cell-specific binding moiety comprises:

(i) a DNA binding domain; and

(ii) a cell-specific ligand that confers on the recombinant cell-specific binding moiety an enhanced ability to bind to the target cell, as compared to the cell-specific ligand encoded by the first and second forms of the additional nucleic acid.

66. A composition for eliciting an immune response that comprises a recombinant cell-specific binding moiety of claim 65.

67. A composition for eliciting an immune response that comprises a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2, wherein the recombinant cell-specific binding moiety comprises:

(i) a DNA binding domain; and

(ii) a cell-specific ligand that confers on the recombinant cell-specific binding moiety an enhanced ability to bind to the target cell, as compared to the cell-specific ligand encoded by the first and second forms of the additional nucleic acid.--

## APPENDIX B

## CLAIMS PENDING IN USSN 09/247,866 WITH ENTRY OF THIS AMENDMENT

1. (Amended) A method for producing and screening a cell-specific binding molecule for an ability to increase uptake or specificity of a genetic vaccine for a target cell, the method comprising:

creating a library of recombinant polynucleotides by recombining at least one nucleic acid that encodes a polypeptide that comprises a nucleic acid binding domain and at least one nucleic acid that encodes a polypeptide that comprises a cell-specific binding domain; and

screening at least one member of the library for a recombinant polynucleotide that encodes a binding molecule that can bind to a nucleic acid and to a cell-specific receptor.

2. (Twice Amended) A method for producing and screening a recombinant cell-specific binding moiety for an ability to increase uptake or specificity of a genetic vaccine for a target cell, the method comprising:

(1) recombining at least first and second forms of at least one nucleic acid, wherein each of the first and second forms of the nucleic acid comprises a polynucleotide that encodes a nucleic acid binding domain and at least first and second forms of at least one additional nucleic acid, wherein each of the first and second forms of the additional nucleic acid comprises a polynucleotide that encodes a cell-specific ligand that specifically binds to a protein on the surface of a cell of interest, wherein the first and second forms of each nucleic acid differ from each other in two or more nucleotides, to produce a library of recombinant binding moiety-encoding nucleic acids;

(2) producing a library of vectors from the library of recombinant binding moiety-encoding nucleic acids, wherein each vector comprises: a) a binding site specific for the nucleic acid binding domain and b) a member of the library of recombinant binding moiety-encoding nucleic acids;

(3) introducing one or more members of the library of vectors into one or more host cells, wherein the encoded recombinant binding moiety is expressed and recovering the expressed recombinant binding moiety;

(4) binding the expressed recombinant binding moiety to a vector comprising the binding site to form a vector-binding moiety complex;

(5) contacting the vector-binding moiety complex with a target cell of interest; and

(6) determining if one or more target cells contain a vector from the vector-binding moiety complex , and recovering the recombinant cell-specific binding moiety nucleic acid from any such target cells.

3. (Twice Amended) The method of claim 2, wherein the method further comprises:

(7) recombining at least one recombinant binding moiety-encoding nucleic acid of (6) with a further form of the polynucleotide that encodes a nucleic acid binding domain and/or a further form of the polynucleotide that encodes a cell-specific ligand, which are the same or different from the first and second forms, to produce a further library of recombinant binding moiety-encoding nucleic acids;

(8) producing a further library of vectors from the further library of recombinant binding moiety-encoding nucleic acids, wherein each vector in the further library of vectors comprises: a) a binding site specific for the nucleic acid binding domain and b) a member of the further library of recombinant binding moiety-encoding nucleic acids;

(9) introducing one or more members of the further library of vectors into one or more host cells, wherein the encoded recombinant binding moiety is expressed and recovering the expressed recombinant binding moiety;

(10) binding the expressed recombinant binding moiety of (9) to a vector comprising the binding site to form a vector-binding moiety complex;

(11) contacting the vector-binding moiety complex of (10) with a target cell of interest and determining if one or more target cells contain a vector from the vector-binding moiety complex of (10);

(12) recovering the recombinant binding moiety-encoding nucleic acid from any such target cells of (11); and

(13) repeating (7) through (12) to screen for a cell-specific binding moiety useful for increasing uptake or specificity of a genetic vaccine vector for a target cell.

4. (Amended) The method of claim 2, wherein the method comprises screening for one or more cell-specific binding moieties that increase uptake of a genetic vaccine vector by the target cells.

5. (Amended) The method of claim 2, wherein the nucleic acid binding domain is a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an E. coli CAP protein, myc, a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a Cys3His (SEQ ID NO:6) box.

6. The method of claim 2, wherein the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV *tat* and HIV *rev*.

7. (Amended) The method of claim 2, wherein the target cell of interest is selected from the group consisting of muscle cells, monocytes, dendritic cells, B cells, T cells, Langerhans cells, keratinocytes, M-cells, liver cells and epithelial cells.

8. (Amended) The method of claim 7, wherein the target cell of interest is a professional antigen presenting cell.

9. The method of claim 8, wherein the antigen presenting cell is a dendritic cell, a monocyte/macrophage, a B cell, or a Langerhans cell.

10. (Amended) The method of claim 8, wherein the cell-specific ligand comprises a polypeptide derived from a protein selected from the group consisting of CD2, CD28, CTLA-4, CD40 ligand, fibrinogen, ICAM-1, Fc portion of immunoglobulin G, and a bacterial enterotoxin, or a subunit thereof.

11. The method of claim 2, wherein the target cell of interest is a human cell.

12. (Amended) The method of claim 2, wherein target cells that contain the vector are identified by selecting for expression of a selectable marker contained in the vector.

13. (Amended) The method of claim 2, wherein each recombinant binding moiety-encoding nucleic acid comprises a genetic vaccine vector.

14. (Twice Amended) A recombinant cell-specific binding moiety produced by expressing in a host cell a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2, wherein the recombinant cell-specific binding moiety comprises:

(i) a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an E. coli CAP protein, myc, a protein having a leucine zipper, a

protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a $Cys_3His$ (SEQ ID NO:6) box or the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV tat and HIV rev; and

(ii) a cell-specific ligand that confers on the recombinant cell-specific binding moiety an enhanced ability to bind to the target cell, as compared to the cell-specific ligand encoded by the first and second forms of the additional nucleic acid.

15. (Amended) A composition for eliciting an immune response that comprises a recombinant cell-specific binding moiety of claim 14.

16. (Twice Amended) A composition for eliciting an immune response that comprises a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2, wherein the recombinant cell-specific binding moiety comprises:

(i) a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an E. coli CAP protein, myc, a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a $Cys_3His$ (SEQ ID NO:6) box or the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV tat and HIV rev; and

(ii) a cell-specific ligand that confers on the recombinant cell-specific binding moiety an enhanced ability to bind to the target cell, as compared to the cell-specific ligand encoded by the first and second forms of the additional nucleic acid.

17. (Twice Amended) A composition for eliciting an immune response that comprises:

a) a recombinant binding moiety that comprises a nucleic acid binding domain and a cell-specific ligand, and

b) a polynucleotide sequence that is capable of expressing an antigen and that comprises a binding site, wherein the nucleic acid binding domain is capable of specifically binding to the binding site.

18. (Three Times Amended) A method for producing and screening a recombinant cell-specific binding moiety for an ability to increase uptake, efficacy, or specificity of a vaccine or antigen for a target cell, the method comprising:

(1) recombining at least first and second forms of at least one nucleic acid, wherein each of the first and second forms of the nucleic acid comprises a polynucleotide which encodes a binding moiety of an enterotoxin, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant nucleic acids;

(2) producing a library of vectors from the library of recombinant nucleic acids, wherein each vector comprises a member of the library of recombinant nucleic acids;

(3) introducing one or more members of the library of vectors into one or more host cells, wherein the member of the library of recombinant nucleic acids is expressed to form a recombinant cell-specific binding moiety polypeptide and recovering the recombinant cell-specific binding moiety polypeptide;

(4) contacting the recombinant cell-specific binding moiety polypeptide with a cell surface receptor of a target cell; and

(5) determining if the recombinant cell-specific binding moiety polypeptide exhibits enhanced ability to bind to the target cell.

19. (Amended) The method of claim 18, wherein the cell surface receptor is present on the surface of a target cell during said contacting.

20. The method of claim 18, wherein the cell surface receptor is $G_{M1}$.

21. The method of claim 18, wherein the host cell is a *V. cholerae* cell which is incapable of expressing CT-A.

22. (Amended) A method for producing a composition for eliciting an immune response, the method comprising coating a polynucleotide that is capable of expressing an antigen with a recombinant cell-specific binding moiety produced by the method of claim 18.

23. (Amended) The method of claim 18, wherein the recombinant cell-specific binding moiety polypeptide is expressed as a fusion protein on the surface of a replicable genetic package.

51. (Amended) A method for producing and screening a recombinant cell-specific binding moiety polypeptide for an ability to increase uptake, efficacy, or specificity of a polypeptide antigen for a target cell, the method comprising:

(1) recombining at least first and second forms of at least one nucleic acid that comprises a polynucleotide which encodes a cell-specific binding moiety, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant nucleic acids;

(2) introducing one or more members of a library of vectors, each of which comprises a member of the library of recombinant nucleic acids, into one or more host cells, wherein the member of the library of recombinant nucleic acids is expressed to form a recombinant cell-specific binding moiety polypeptide;

(3) contacting the recombinant cell-specific binding moiety polypeptide with a cell surface receptor of a target cell;

(4) determining if the recombinant cell-specific binding moiety polypeptide exhibits enhanced ability to bind to the target cell; and

(5) fusing or linking the recombinant cell-specific binding moiety polypeptide to the polypeptide antigen or coating the polypeptide antigen with the recombinant cell-specific binding moiety polypeptide.

53. (Amended) The method of claim 51, wherein the recombinant cell-specific binding moiety polypeptide is fused or linked to the polypeptide antigen.

54. (Amended) The method of claim 51, wherein the target cell is selected from the group consisting of muscle cells, monocytes, dendritic cells, B cells, T cells, Langerhans cells, keratinocytes, M-cells, liver cells and epithelial cells.

55. (Amended) The method of claim 51, wherein the cell surface receptor is present on the surface of a target cell during said contacting.

56. (Amended) The method of claim 51, wherein the cell-specific binding moiety comprises a polypeptide derived from a protein selected from the group consisting of selected from the group consisting of CD2, CD28, CTLA-4, CD40, and ligands thereof; fibrinogen; factor X; ICAM-1; β-glycan; Fc portion of immunoglobulin G; and a bacterial enterotoxin, or a subunit thereof.

57. (Twice Amended) A method for producing a composition for eliciting an immune response, said method comprising coating the polypeptide antigen with a recombinant cell-specific binding moiety polypeptide produced by the method of claim 51.

58. (Twice Amended) A composition for eliciting an immune response comprising an antigen and a recombinant cell-specific binding moiety polypeptide, wherein the composition is produced by the method of claim 51, wherein:

(i) the antigen comprises a polypeptide antigen;

(ii) the recombinant cell-specific binding moiety polypeptide exhibits enhanced ability to bind to the target cell; and

(iii) the polypeptide antigen and the recombinant cell-specific binding moiety polypeptide are derived from different polypeptides.

59. (Amended) The method of claim 2, wherein the binding site of each vector is derived from a binding site present in at least one form of at least one nucleic acid of (1).

60. The method of claim 2, wherein the binding site is joined to the member of the library of recombinant binding moiety-encoding nucleic acids after said recombining.

61. (Amended) The method of claim 2, wherein the vector-binding moiety complex forms inside the host cell and, prior to the contacting of (5), the host cell is lysed under conditions that do not disrupt the vector-binding moiety complex.

62. (Amended) The method of claim 3, wherein the vector-binding moiety complex of (10) forms inside the host cell and, prior to the contacting of (11), the host cell is lysed under conditions that do not disrupt the vector-binding moiety complex.

63. The method of claim 2, wherein the cell-specific ligand comprises a polypeptide derived from a protein selected from the group consisting of CD2, CD28, CTLA-4, CD40, and ligands therefor; fibrinogen; factor X; ICAM-1; β-glycan; Fc portion of immunoglobulin G; and a bacterial enterotoxin, or a subunit thereof.

64. The method of claim 51, wherein the polypeptide antigen is coated with the recombinant cell-specific binding moiety polypeptide.

65. A recombinant cell-specific binding moiety produced by expressing in a host cell a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2, wherein the recombinant cell-specific binding moiety comprises:

(i) a DNA binding domain; and

(ii) a cell-specific ligand that confers on the recombinant cell-specific binding moiety an enhanced ability to bind to the target cell, as compared to the cell-specific ligand encoded by the first and second forms of the additional nucleic acid.

66. A composition for eliciting an immune response that comprises a recombinant cell-specific binding moiety of claim 65.

67. A composition for eliciting an immune response that comprises a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2, wherein the recombinant cell-specific binding moiety comprises:

(i) a DNA binding domain; and

(ii) a cell-specific ligand that confers on the recombinant cell-specific binding moiety an enhanced ability to bind to the target cell, as compared to the cell-specific ligand encoded by the first and second forms of the additional nucleic acid.